APPENDIX A

Prescribing in liver disease

Munir Pirmohamed

What's new?

- Information is now accumulating to show that even moderate degrees of liver impairment can affect renal function, requiring changes in the doses of renally eliminated drugs. The mechanisms of this are unclear, and require further investigation.

Abstract

Patients with liver disease often require drug therapy. Since the liver is the main site of drug detoxification and elimination in the body, patients must be carefully assessed for the need for therapy. If a drug is needed for a patient with liver disease, the choice of drug, its dose, and duration of therapy must be carefully considered in order to avoid adverse effects. Ideally, in patients with liver disease, it is better to choose a drug that has a large therapeutic index, is largely devoid of pharmacokinetic and pharmacodynamic interactions, is devoid of hepatotoxic effects and is renally eliminated. However, the ideal drug with these properties is often not available, and in such cases, the dose and drug should be individualized to the patient, who should then be carefully monitored, and the drug used for the shortest period possible. The *British National Formulary* contains useful information on drugs that need to be either avoided or dose modified in patients with liver disease.

Keywords hepatotoxic drugs; liver disease; pharmacodynamics; pharmacokinetics; prescribing

Patients with liver disease often require drug treatment, either for their liver disease and its complications, or for other concomitant conditions. Liver disease has major effects on drug response of which the prescriber should be aware to ensure safe and effective therapy.

The liver and drug metabolism

The liver is the main site of drug metabolism. This is primarily a detoxification mechanism whereby the body converts pharmacologically active lipid-soluble drugs into inactive hydrophilic metabolites, which can then be excreted by the kidneys. On occasions, metabolic enzymes are also needed for conversion of pro-drugs to their active components. While metabolism in the liver is important for lipid-soluble drugs, renal excretion is more important for hydrophilic drugs (Figure 1). As a general rule, therefore, drugs that undergo hepatic metabolism are more likely to require dose alteration (of either the loading or maintenance dose or both) in patients with liver impairment than those drugs that predominantly undergo renal excretion, although there are exceptions (see below).

Drug disposition is determined by three phases (Figure 1), as follows.

- Phase I pathways are metabolic reactions catalysed by a superfamily of cytochrome P450 enzymes located in the endoplasmic reticulum. Each P450 isoenzyme varies in terms of expression and substrate specificity (Table 1).
- Phase II reactions are performed by various enzymes including the glucuronyl transferases, N-acetyl transferases and glutathione-S-transferases, which are located in both the endoplasmic reticulum and the cytosol.
- The phase III pathway is represented by active drug transport processes across cellular membranes rather than enzyme-catalysed reactions; these include both efflux (e.g. P-glycoprotein) and influx (e.g. organic anion transporters) transporters.

Effect of liver disease on pharmacokinetics: the effect of liver disease on drug metabolism depends on various factors, including:

- the severity of the liver disease – because of the enormous reserve of the liver parenchyma, impaired hepatic elimination of drugs occurs only in severe disease
- the enzyme responsible for drug metabolism – in general, phase II metabolic enzymes are affected to a lesser extent than phase I enzymes; the effect on the different P450 isoforms also varies (Table 1)
- the type of liver disease – a cholestatic pattern is more likely to affect drug transporter proteins (phase III pathways), whereas phase I metabolism is relatively spared; in contrast, acute

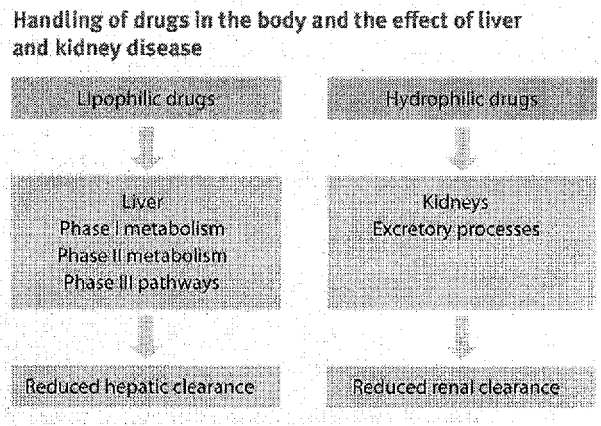

Figure 1

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Cytochrome P450 isoforms involved in phase I drug metabolism in humans

P450 isoform	Substrates	Effect of liver disease on P450 activity
• CYP1A2	Clozapine, theophylline	↓↓↓
• CYP2A6	Halothane, methoxyflurane	↓↓
• CYP2C9	Diclofenac, losartan, warfarin	↓
• CYP2C19	Citalopram, diazepam, omeprazole	↓↓↓
• CYP2D6	Codeine, haloperidol, metoprolol, nortriptyline	↔
• CYP2E1	Enflurane, halothane, paracetamol	↓
• CYP3A4	Amiodarone, carbamazepine, ciclosporin, terfenadine	↓↓

Only a few substrates are listed for each P450 isoform.

Table 1

hepatic inflammation is more likely to down-regulate P450 enzyme expression via a nitric oxide-dependent pathway.

A decrease in hepatic clearance may result in increased drug levels and potential toxicity (Figure 2), particularly for drugs with a narrow therapeutic index. For pro-drugs, reduced conversion to the active compound results in a reduced effect.

Other effects: liver disease can also affect drug pharmacokinetics through other mechanisms, as follows.

Changes in drug absorption – gut motility is altered in patients with cirrhosis, probably as a result of abnormal levels of gut hormones such as motilin. The net result is a delay in gastric emptying and orocaecal transit, resulting in a reduction in the rate but not the extent of absorption. This may be particularly important for delayed release compounds where the action of these drugs will be delayed further.

Changes in drug distribution – chronic liver disease is characterized by hypoproteinaemia. This may result in a higher fraction of free drug particularly when the degree of protein binding is high. The clinical importance of this may only be manifest in patients with severe liver impairment because of the high metabolic reserve of the liver. The volume of distribution of hydrophilic drugs, such as digoxin, will be increased in patients with oedema and/or ascites; this may require the use of higher loading doses (based on the patient's weight), but maintenance doses may not need to be changed unless renal function is also affected.

Changes in liver blood flow – blood flow to the liver may be decreased generally or may bypass the liver as a result of portosystemic shunting in patients with cirrhosis. The effect of this depends on the drug and its degree of extraction by the liver; in general, the higher the extraction by the liver, the more important is blood flow (in relation to metabolism) in determining pharmacokinetics. High extraction drugs will therefore show a marked increase in bioavailability; for example, the bioavailability of chlormethiazole increases by 90% which leads to a 10-fold higher drug exposure with the risk of toxicity. With such drugs, both the loading and maintenance doses need to be decreased.

Changes in renal excretion – renal elimination of hydrophilic drugs (or hydrophilic metabolites) is affected in patients with severe and rapidly advancing hepatic disease who develop hepatorenal syndrome. However, it is becoming clear that even moderate hepatic impairment (through mechanisms that are unclear) reduces renal clearance, necessitating a reduction in the dose of renally eliminated drugs. Serum creatinine is an insensitive marker of glomerular filtration rate in patients with cirrhosis because of the reduced muscle mass and reduced conversion of creatine to creatinine in the liver; creatinine clearance should be measured, but even this can over-estimate glomerular filtration in patients with cirrhosis.

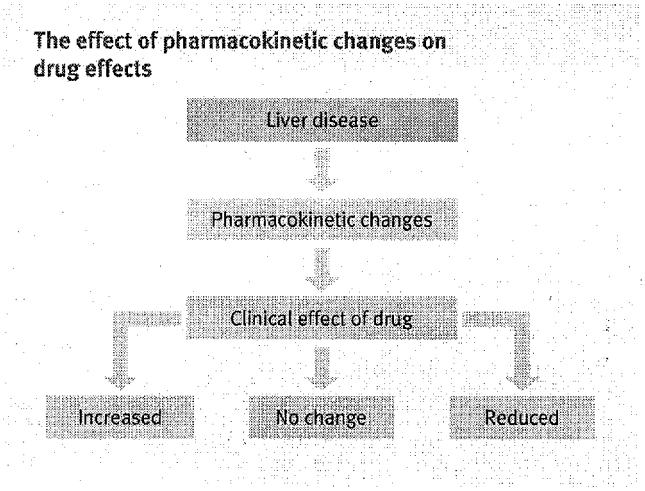

Figure 2

Effect of liver disease on drug pharmacodynamics

Drug response in liver disease is also determined by pharmacodynamic changes. These can result in increased or decreased sensitivity, or an increased risk of toxicity (Figure 3), through changes in the function of other organs such as the brain and kidneys.

Use of potentially hepatotoxic drugs

There is no evidence that patients with liver disease are at increased risk of further liver damage when administered drugs known to cause idiosyncratic hepatotoxicity. However, in view of the reduced hepatic reserve, any liver damage induced by the drug may have more severe clinical consequences. With dose-dependent hepatotoxins, use of high doses on either one occasion (e.g. paracetamol overdose) or cumulatively (e.g. methotrexate) increases the risk of liver toxicity in patients with pre-existing liver impairment.

General rules for prescribing in liver disease

Patients must be assessed carefully before prescription of any drug, to determine the risks and benefits. Several factors must be considered.

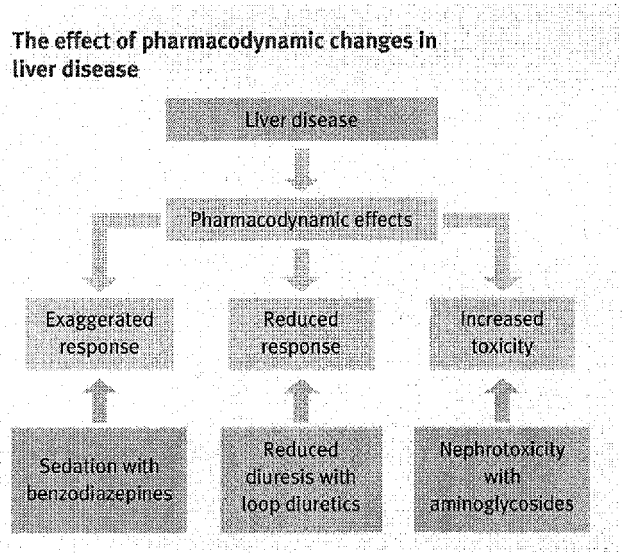

Figure 3

- How serious is the condition that needs to be treated and what are the consequences of withholding treatment?
- What drug treatments are available?
- Are the efficacies of the different treatments equivalent?
- What are the adverse effects of the different treatments?

When several drugs are available to treat the same condition, the drug with the largest therapeutic index should be chosen. However, given the major changes in pharmacokinetic and pharmacodynamic parameters seen in patients with liver disease, the therapeutic index may not be equivalent to that in patients without liver disease. Therefore, it is also important to consider other factors.

- Is the drug metabolized by the liver? Hepatic impairment reduces the clearance of such drugs. For those with a narrow therapeutic index (e.g. phenytoin, theophylline), there is a disproportionate increase in drug levels and hence toxicity, and a reduction in dose is therefore necessary. However, unlike in renal failure, there is no easy means of calculating the required change in those with hepatic impairment; further dose changes are dictated by both the therapeutic response and adverse effects and therapeutic drug monitoring, when available. Table 2 lists some of the drugs requiring dose reduction in liver disease; a more complete list is available in the *British National Formulary*.
- Does the drug have a high hepatic extraction ratio? Liver blood flow is a major pharmacokinetic determinant for such drugs, and reduces first-pass metabolism. A reduction in dose of the oral, but not the parenteral, formulation is required. Chlormethiazole, which is used for alcohol withdrawal, is a typical example; in cirrhotic patients, first-pass metabolism is reduced, and the resulting high drug levels may cause respiratory depression.
- Will the drug worsen the pharmacodynamic changes seen in liver disease? Specific examples and mechanisms are shown in Table 2. Non-steroidal anti-inflammatory drugs (NSAIDs) enhance sodium and water retention and worsen ascites, and the effects on platelets, combined with clotting defects, increase the risk of bleeding. Bleeding into the gastrointestinal tract may also precipitate encephalopathy. Because of the changes in renal function in liver disease, NSAIDs affect intrarenal vasodilatory prostaglandins, and in some patients precipitate renal failure.
- Is the drug potentially hepatotoxic? Drug-induced liver damage has more severe clinical consequences in patients with hepatic impairment. Therefore, if a non-hepatotoxic drug is available, this should be used in preference.

Drugs that should be avoided or dose reduced in hepatic disease

Hepatic clearance decreased
- High extraction ratio drugs
- Phenytoin
- Theophylline

Inhibit clotting factor synthesis
- Warfarin
- Phenindione

Lead to excess sodium and water retention
- Corticosteroids
- Non-steroidal anti-inflammatory drugs

Lead to potassium loss
- Corticosteroids
- Diuretics

May precipitate hepatic encephalopathy
- Hypnotics/sedatives
- Lithium
- Loop diuretics
- Opiates

Enhanced risk of adverse drug reaction
- Angiotensin-converting enzyme inhibitors (hypotension)
- Aminoglycosides (nephrotoxicity)
- Cimetidine (confusion)
- Non-steroidal anti-inflammatory drugs (gastrointestinal bleeding)
- Oral hypoglycaemic agents (hypoglycaemia)
- Quinolone antibiotics (CNS toxicity)

Table 2

In keeping with good clinical practice, all patients taking drugs should be monitored carefully; the frequency and form of monitoring depends on the drug, condition being treated and the severity of the liver disease. It is important to prescribe simple regimens and to avoid drugs that interact (the consequences of interaction may be more severe in these patients). Patients should be informed why the drug is being used and given instructions on whom to contact if they develop adverse effects or their condition deteriorates. It is also important to review the patient regularly, and not to be afraid of stopping drug therapy. Drugs should always be considered in the differential diagnosis in patients who develop new symptoms and signs. ◆

FURTHER READING

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(*Includes an interesting section on the mechanisms of impairment of drug elimination in liver disease.*)

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(*Comprehensive article detailing the latest aspects of drug metabolism in liver disease, with sections on individual P450 isoforms and drugs.*)

Practice points

- Liver disease affects both pharmacokinetic and pharmacodynamic parameters, both of which increase the risk of adverse drug reactions
- Doses of lipophilic drugs should be reduced, particularly for those with a narrow therapeutic index
- First-pass metabolism of drugs with high hepatic extraction is reduced, necessitating a reduction in the loading and maintenance doses of oral formulations
- Start at low doses, increasing the dose with careful monitoring; avoid concomitant use of drugs that interact – the effects are more severe in these patients
- Choose a hydrophilic drug over a lipophilic compound when available
- The effects of drug-induced hepatotoxicity are more severe in patients with liver disease because of reduced hepatic reserve